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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,506	11/09/2000	Arno Hartmann	MERCK-2056	2626

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,506	HARTMANN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-11,13,16-18 and 24-29* is/are pending in the application.

4a) Of the above claim(s) *8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10,11,13,16-18 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment filed 26 September 2003 has been entered in full. Claims 6, 7, 12, 14, 15 and 19-23 were cancelled. Claims 8 and 9 were withdrawn. Claims 1-5, 10, 11, 13, 16-18, 24-29 are under examination.

The information disclosure statement filed 12 November 03 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The specification is in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations.

The Examiner has acknowledged that cancellation of non-elected species is not, as yet, required. This is in reference to the objection of claims 1, 10, 17 and 18 and the 35 USC 112, second paragraph rejection of claims 1, 5 and 16, set forth at page 4 of the previous Office Action, 27 March 2003.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 1-5, 16-18, 24 and 25 under 35 U.S.C. 102(a) as being anticipated by Sytkowski *et al.*, WO 99/02709 as set forth at pages 5-6 of the previous Office Action (27 March 2003) is *withdrawn* in view of Applicants' arguments (26 September 2003).

The rejection of claims 10-13 under 35 U.S.C. 103(a) as being anticipated by Sytkowski *et al.*, WO 99/02709 in view of Okasinski *et al.*, US Patent No. 5,888,772 as set forth at pages 6-8 of the previous Office Action (27 March 2003) is *withdrawn* in view of Applicants' arguments (26 September 2003).

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.** The specification as originally filed does not provide support for the invention as now claimed:(claims 1 and 26)"Fcm-L-EPOm" and (claim 1) "EPOm is EPO which is mutated in its amino acid sequence and comprises at least one of the following changes".

Page 6, lines 5-25 discloses the modified EPO proteins, however, there is not support in the specification for Fcm-L-EPOm.

Page 9, lines 27-28 discloses the properties of EPOm, but there is not support in the specification for EPOm which is *only* mutated. The specification teaches that EPOm is EPO which is mutated but not truncated. Lastly, page 10,

lines 3-7 teaches the changes made in EPOm. The specification states, "wherein in the EPOm portion at least one of the following changes are achieved...". There is not support in the specification for "and comprises at least one of the following changes".

Applicant's amendment, filed 26 September 2003, asserts that no new matter has been added and directs support to pages at page 10, line 31-page 11, lines 5 and page 10, lines 1-6 and original claim 6 for the written description for the above-mentioned "limitations". The exact wording or connotation of the instant claims is not readily apparent from said sections.

The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, applicant is invited to provide specific/sufficient written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Specification

The amendment filed 26 September 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "Fcm-L-EPOm" and "EPOm is EPO which is mutated in its amino acid sequence and comprises at least one of the following changes" .

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

Claims 1, 26-29 (and dependent claims 2-5, 10, 11, 13, 16-18, 24 and 25) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a fusion protein comprising an Fc portion of an Ig molecule and an EPO molecule, wherein said Fc portion is fused covalently via its C-terminus directly or indirectly to said EPO molecule and the Fc portion as well as the EPO portion may be modified or mutated, wherein said fusion protein is Fc-EPOm, wherein the EPOm is derived from human EPO and has the following mutations His32→Gly, Cys33→Pro and Trp88→Cys, does not reasonably provide enablement for:

(claim 1) a fusion protein comprising an Fc portion of an Ig molecule and an EPO molecule, wherein said Fc portion is fused covalently via its C-terminus directly or indirectly to said EPO molecule and the Fc portion as well as the EPO portion may be modified or mutated, wherein said fusion protein is Fc-EPOm, wherein the EPOm comprises at least one of the following changes:Asn24,38,83 →Gln, Ser126→Ala, His32→Gly, Ser34 →Arg and Pro90 →Ala or

(claim 26) a fusion protein comprising an Fc portion of an Ig molecule and an EPO molecule, wherein said Fc portion is fused covalently via its C-terminus directly or indirectly to said EPO molecule and Fc portion as well as the EPO portion may be modified or mutated, wherein EPOm comprises Cys at position

88 and at least one of the following amino acid variations: position 29 is not Cys, position 33 is not Cys, and position 139 is Cys or

(claim 27) wherein EPOm is derived from human EPO and has at least one of the following mutations: His32→Gly, Ser34→Arg, and Pro90→Ala or

(claim 28) wherein the EPOm comprises cysteines at positions 29 and 88 or (claim 29) wherein the EPOm comprises cysteines at positions 29, 33, 88 and 139.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are drawn to Fc-EPOm (species elected by Applicant) with an *unlimited* amount of amino acid substitutions/mutations in the EPO sequence. The specification teaches the construction and expression of an Fc-EPO variant termed Fc-EPO (Cys29-Cys88) (page 35, Example 13, lines 5-16). The specification teaches that alterations His32Gly, Cys33Pro, Trp88Cys and Pro90Ala were introduced into human Fc-EPO by standard site-directed mutagenesis techniques (page 35, lines 9-11). The activity of the Fc-EPO (Cys29-Cys88) variant was tested by proliferation assays (page 35, lines 17-18), *in vivo* and long term stability studies (page 37, lines 26-33).

As was stated above, the specification teaches that alterations His32Gly, Cys33Pro, Trp88Cys and Pro90Ala were introduced into human Fc-EPO by standard site-directed mutagenesis techniques to make Fc-EPO (Cys29-Cys88), *however*, this is incorrect. The specification teaches the sequence of Fc-EPO

(Cys29-Cys88) on page 37, line 15. The amino acid at position 90 is still a proline; not changed to an alanine as was recited on page 35, lines 10-11 (Pro90Ala). Thus only alterations His32Gly, Cys33Pro and Trp88Cys were made in Fc-EPO to make Fc-EPO (Cys29-Cys88). The specification discloses other EPO variants, but it is not predictable that these variants would have similar biological activity as compared to Fc-EPO (Cys29-Cys88) because there is no guidance regarding which residues of EPO are critical to retain function and which residues may be changed without affecting function.

The instant specification could not support claims to EPO polypeptides modified to an unlimited extent relative to those exemplified because as the number of modified sites increases, the number of possible variants, and hence the degree of experimentation required, increases exponentially. Additionally, as plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. The instant claims recite various properties such as improved biological activity, extended serum half-life and greater specific activity than the comparable Fc-EPO fusion proteins having no mutated EPO molecules. It is in no way predictable that the mutations, deletions, *etc.* as recited in the instant claims would afford a protein having activity comparable to the one disclosed absent guidance regarding where and what kind of mutations predictably result in such.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the

protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. The ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517 and Ngo *et al.*, 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 433-440 and 492-495). Okasinski *et al.*, US Patent 5,88,722 (cited in previous Office Action) teach that a mutation at residue 33 (change from Cys to Pro at residue 33), substantially eliminated erythropoietin activity (column 4, lines 33-44), however a second mutation in the same protein (change from Arg to Cys at residue 139) completely restored erythropoietin activity (column 16, lines 51-57 and column 25, lines 3-8). Okasinski *et al.* also disclose references, which teach mutations in erythropoietin that reduce or completely eliminate biological activity (column 3, lines 6-27). Thus the changes which can be made in the structure and still maintain sufficient activity is

unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically large number of possible structural variants had the functional properties of the claimed proteins.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
December 30, 2003

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